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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
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1655

DATE MAILED: 12/04/2001

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/760,819

Applicant(s)

STANLEY, CHRISTOPHER J.

Examiner

Frank W Lu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-22 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 January 2001 (original) is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 09/313,385.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Location of Application

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1655.

Priority

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Drawings

3. The drawings are objected to for reasons as stated on FORM PTO-948 (Rev. 8-98). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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5. Claims 1-17, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using Dextran as a carrier for a primer in the replication of a nucleic acid template, does not reasonably provide enablement for using any kind of macromolecule as a carrier for a primer in the replication of a nucleic acid template. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance in the specification to show that any kind of macromolecule such as any kind of protein or agarose derivative can be used as a carrier for a primer in the replication of a nucleic acid template. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether any kind of macromolecule can be used as a carrier for a primer in the replication of a nucleic acid template without inhibiting a DNA polymerase activity.

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The invention relates to a process for the replication of a nucleic acid template in the presence of a primer that is bound to any kind of carrier macromolecule. The specification provides working examples (see pages 14-18) to show a process for PCR of a nucleic acid template in the presence of a primer that is bound to Dextran. In fact, not any kind of macromolecule can be used as a carrier for a PCR primer in PCR reaction without inhibiting a DNA polymerase activity. For example, it is known that both Hb and agarose are potential inhibitors of DNA polymerases (see Nucleic Acids Res., 18, 5908, 1990 and Molecular Cloning: A Laboratory Manual, page 164, 1982). Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. See M.P.E.P. §§ 706.03(n) and 706.03(z).

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 20 is rejected as vague and indefinite because it is unclear what it intended. For example, does this phrase "such that said probe comprises said extended primer having a sequence complementary to said sequence to be detected bound to said carrier macromolecule" mean that said probe comprising said extended primer having a sequence complementary to said sequence to be detected bound to said carrier macromolecule" or mean something else? Is said

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carrier macromolecule in the sample for the detection? Does the phrase "therefrom" mean "therefore" or mean something else?"

9. Claim 22 provides for the use of an immobilized nucleic acid, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 22 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claims 1-6, 8, 9, 11, 13, 17, 21, and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Belyavsky *et al.*, (US Patent No. 5,814,445, filed on July 11, 1995).

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Regarding claims 1, 3, 4, 8, 9, 11, and 13, for cloning of the differentially expressed sequences (a cDNA fragment), the corresponding bands of gel (containing a DNA fragment) were cut apart and eluted from the gel in a buffer at pH 8. Then the fragments were precipitated with three volumes of 96% ethanol using glycogen as carrier (considered substantially uncharged at pH 8 as recited in claim 4). Finally the precipitated fragment (template) was further amplified by PCR as recited in claims 8 and 9 (see columns 7 and 8). Note that: (1) since the precipitated fragment used for PCR bound to glycogen, the first and second primers could be considered to indirectly bind to glycogen after the primer annealed with the fragment as recited in claims 1 and 13; and (2) the fragment was double stranded and denature to single stranded in PCR denaturation step in order to annealing with the primer as recited in claim 11.

Regarding claims 2 and 4-6, these properties as recited in claims can be considered to be inherent to glycogen since glycogen was a water soluble synthetic polysaccharide having a branched-chain structure (considered as substantially linear) and a molecule weight from 2,270,000 to 3,500,000 (see The Merck Index, 8th Edition, page 501, left column).

Regarding claim 17, DNA fragment cut from the gel and used for PCR was from mRNA of mouse thymus and spleen (see example in column 7).

Regarding claim 21 and 22, although Belyavsky *et al.*, did not directly show that glycogen (macromolecule) was bound to a solid support as recited in claims 21 and 22, in the absence of convincing evidence to the contrary, this limitation is considered to be inherent to the reference taught by Belyavsky *et al.*, since it was known that a complex of the DNA fragment and glycogen was pelleted on the bottom of a centrifuge tube (considered as a solid support as recited in claim

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21) during the precipitation process. The precipitated DNA fragment could be used as a primer or probe recited in claim 22.

Therefore, Belyavsky *et al.*, teach all limitations recited by claims 1-6, 8, 9, 11, 13, 17, 21, and 22.

12. Claims 1, 4, 6, 8, 9, 11, 12, 15, 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee *et al.*, (BioTechniques, 14, 191 and 192, 1993).

Lee *et al.*, teach DNA sequencing using biotinylated single-stranded DNAs bound to Dynabeads. A double PCR product immobilized on the beads was denatured to a single stranded DNA before the sequencing reaction as recited in claim 11 (see pages 191 and 192). Note that: (1) The biotin molecule and the bead here could be considered as a carrier macromolecule and a solid support respectively as recited in claims 1 and 12; (2) since a sequencing primer annealed with a biotinylated single-stranded DNA in sequencing reaction, the primer could be considered to indirectly bind to the carrier macromolecule as recited in claim 1; (3) biotin molecule could be considered as water soluble, substantially linear and substantially uncharged at pH from 4 to 10 as recited in claims 4 and 6; (4) the process of the sequencing reaction could be considered to meet the limitations as recited in claims 8 and 9; (5) ^{35}S -dATP could be considered as a detection marker for the sequencing reaction as recited in claim 15; and (6) biotinylated single-stranded DNAs immobilized on Dynabeads could be considered as an immobilized nucleic acid as recited in claims 21 and 22. This biotinylated single-stranded DNA could be used as a probe as recited either a primer or probe as recited in claim 22.

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Therefore, Lee *et al.*, teach all limitations recited by claims 1, 4, 6, 8, 9, 11, 12, 15, 21 and 22.

13. Claims 1, 4, 6, 8, 9, 11, 15, 17-19, 21, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Conrad (US Patent No. 5,652,099, filed on August 18, 1994).

Regarding claims 1, 4, 6, 8, 9, 11, 15, 18, 19, 21, and 22, as shown in Example 4, a poly (AC) template was amplified using the biotinylated synthetic 22-mer primers as recited in claims 8 and 9. The hybridization between biotinylated poly (AC) and fluorescence-labeled poly (FC) probe were detected by quenched fluorescence of the poly (FC) probe. The hybrids could be adsorbed via the biotin moiety to avidinylated beads (see column 27). Note that: (1) biotin could be considered as a carrier macromolecule and a detectable marker as recited in claims 1 and 15; (2) biotin molecule could be considered as water soluble, substantially linear and substantially uncharged at pH from 4 to 10 as recited in claims 4 and 6; (3) the poly (AC) template was double stranded and denature to single stranded in PCR denaturation step in order to annealing with the primer as recited in claim 11; (4) the hybridization between biotinylated poly (AC) and fluorescence-labeled poly (FC) probe could be considered to meet the limitations as recited in claims 18 and 19 since biotin and fluorescence complex could be considered as the first and second carrier macromolecules respectively; and (5) the hybrids of biotinylated poly (AC) and fluorescence-labeled poly (FC) probe immobilized on avidinylated beads could be considered to meet the limitations as recited in claims 21 and 22 since avidinylated beads could be considered

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as a solid support and the hybrids could be used as either a primer or probe as recited in claim 22.

Regarding claim 17, a biological sample could be from bacteria (see example 6 in column 27).

Therefore, Conrad teaches all limitations recited by claims 1, 4, 6, 8, 9, 11, 15, 17-19, 21, and 22.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Conrad (1994) as applied to claims 1, 4, 6, 8, 9, 11, 15, 17-19, 21, and 22 above, and further in view of Nuovo *et al.*, (US Patent No. 5,538,871, filed on February 17, 1995).

The teachings of Conrad have been summarized previously, *supra*.

Conrad does not disclose *in situ* PCR as recited in claim 16.

Nuovo *et al.*, does teach *in situ* PCR (see Examples 1 and 3 in columns 18-22). Note that they labeled PCR product using digoxigenin-11-dUTP (see column 2, third paragraph).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have

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replicated a nucleic acid template *in situ* using a biotin-labeled primer in view of the patent from Nuovo *et al.*. One having ordinary skill in the art would have motivated to modify the methods of Conrad and Nuovo *et al.*, and combine above methods together because the simple replacement of one well known method for labeling a PCR product (i.e., using digoxigenin-11-dUTP) from another well known method for labeling a PCR product (i.e., using biotin-labeled primer, biotin as carrier) during the process of *in situ* PCR would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

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F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,207,385B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in this instant application and U.S. Patent No. 6,207,385B1 are directed to detecting the presence of a nucleic acid and replicating a nucleic acid template. Note that independent claims 1 and 18 in this instant application are much broader than independent claims 1 and 2 in U.S. Patent No. 6,207,385B1 while dependent claims 2-5, 7-11, and 13-17 in this instant application have only slight differences from dependent claims 3-15 in U.S. Patent No. 6,207,385B1.

Conclusion

18. No claim is allowed.

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19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
November 30, 2001


W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600